REMARKS

Claims 1-4, 6-47 and 70-80 remain pending herein.

Claim Rejections under 35 U.S.C. 103(a)

A. Terry in view of Farber and Darouiche

Claims 1-4, 6-8, 13-19 and 72-80 presently rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,596,401 (Terry) in view of U.S. Patent No. 5,366,505 (Farber) and U.S. Patent No. 6,475,434 (Darouiche).

Applicants respectfully traverse this rejection and its supporting remarks.

For example, claims 1 and 72, the only independent claims presently pending, are directed to implantable or insertable medical devices that comprise the following: (a) bioactive agents comprising (i) an antimicrobial agent and (ii) a microbial attachment/biofilm synthesis inhibitor selected from NSAIDs, chelating agents, and mixtures thereof; and (b) at least one biocompatible matrix polymer region that comprises (i) one or more polymers and (ii) one or more of the bioactive agents dispersed throughout. At least one biocompatible matrix polymer region within the device is not a medical device coating. Moreover, the bioactive agents are present in the device in an amount effective to inhibit microbial growth on the device for a period of at least 30 days after implantation or insertion of the device into a subject.

Several of these features are neither taught nor suggested by Terry, Farber and Darouiche.

For example, Terry discloses a variety of hydrophilic silane copolymers for use as medical device *coatings*. See Terry, ABSTRACT and FIELD OF THE INVENTION. Hence, Terry describes the use of active agents within a coating layer, rather than in a matrix polymer region that is *not a medical device coating* as claimed in claims 1 and 72. Indeed it is respectfully submitted that drug release from coatings is the norm for medical devices, whereas release from a non-coating matrix region is more atypical.

Moreover, Terry neither teaches nor suggests medical devices which inhibit microbial growth on the device for a period of at least 30 days after implantation or insertion of the device into a subject, as claimed in claims 1 and 72.

In this regard, the present inventors have found that a device which is intended to remain implanted for a long period of time will generally require high bioactive agent loadings. See, e.g., paragraph [0037] of the present specification. Such high loadings are achieved in the present invention by using at least one biocompatible matrix polymer region, which is not a coating, and which further comprises one or more polymers with one or more bioactive agents dispersed throughout.

Extrusion is a particularly beneficial manufacturing technique for producing such regions in various embodiments of the present invention (see, e.g., claims 73-75 and 77-79), because it is capable of effectively mixing polymer(s) and bioactive agent(s) so as to create matrix polymer regions having bioactive agent(s) dispersed throughout, see, e.g., paragraphs [0012], [0079] and [0082] of the present specification. This is opposed to, for example, matrix polymer regions in which the bioactive agents are partitioned to the surface, see, e.g., paragraphs [0012] and [0077].

Claims 1 and 72 are also directed to medical devices that comprise, in combination, (i) an antimicrobial agent and (ii) a microbial attachment/biofilm synthesis inhibitor selected from NSAIDs, chelating agents, and mixtures thereof.

As described in paragraph [0036] of the present specification:

> The presence of both an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor in a medical device in accordance with the present invention provides distinct advantages over the use of, for example, only an antimicrobial agent. The use of such a dual mechanism for preventing microbial colonization and attachment is believed to have a synergistic effect. The synergy is related to the different mechanism of action of each of the bioactive agents. The antimicrobial agent not only kills a large percentage of microbes approaching a surface of the device, it also reduces the burden of microbes upon which the microbial attachment/biofilm synthesis inhibitor must act. Moreover, microbes that have attached to a surface produce a protective biofilm barrier after attachment. This biofilm barrier prevents or reduces the ability of antimicrobial agents from reaching the microbes. The antimicrobial agent is thereby rendered substantially less effective upon formation of the biofilm barrier. Therefore, if microbial attachment is prevented, biofilm synthesis is inhibited and the antimicrobial agent is rendered more effective.

In contrast to the particular, synergistic combination of active agents claimed in claims 1 and 72, the active agents described for use in conjunction Terry's coatings include a remarkably wide variety agents, including, but not limited to, antimicrobial

agents such as antibacterial agents, antifungal agents, antiviral agents and antibiotics; growth factors; cytokines; immunoglobulins; and pharmaceuticals and nutraceuticals, including, but not limited to, antithrombogenic agents, antitumoral agents, antiangiogenic agents, spermicides, anesthetics, analgesics, vasodilation substances, wound healing agents, plant extracts, and other therapeutic and diagnostic agents. See Terry at col. 13, lines 31-42. Other active agents described for use in conjunction Terry's coatings include herbicides, insecticides, algaecides, antifoulants, antifogging agents, and UV and other screening agents. *Id.*

Although Terry does independently describe certain compounds having antimicrobial activity including chlorhexidine and triclosan (see, e.g., col. 14, line 62 to col. 15, line 19) as well as certain NSAIDs including acetylsalicylic acid, ibuprofen, naproxen, diclofenac, ketoprofen, indomethacin, etc. (see, e.g., col. 15, line 31 to col. 16, line 22), these are only a few of the many, many active agents described in Terry. There is no teaching or suggestion in Terry, however, which would motivate one or ordinary skill in the art to combine these particular groups of compounds for purposes of inhibiting microbial growth on medical devices as claimed in claims 1 and 72.

Farber does not make up for these deficiencies in Terry. For example, Farber teaches against the incorporation of antimicrobial agents for the following reasons: (a) even broad-spectrum antibiotics eventually lead to the selection of resistant organisms, (b) unless the delivery of the antibiotic is rapid, potent, and long lasting, formation of a protective glycocalyx will prevent its effectiveness, and (c) many antibiotics produce allergic reactions in some patients. See, e.g., col. 2, lines 41-55. Consequently, Farber resorts to an *alternative approach* based on interference with the adherence of bacteria to polymeric surfaces of medical devices, thereby eliminating the need for antimicrobials in his devices. See, e.g., col. 2, lines 56-58. Hence, like Terry, Farber neither teaches nor suggests the combination of (i) an antimicrobial agent and (ii) a microbial attachment/biofilm synthesis inhibitor selected from NSAIDs, chelating agents, and mixtures thereof, for purposes of inhibiting microbial growth on the device, as claimed in claims 1 and 72, and in fact teaches away from such a combination.

Nor does Farber teach or suggest medical devices which inhibit microbial growth on the device for a period of at least 30 days after implantation or insertion of the device

into a subject, as claimed in claims 1 and 72. In fact, the discussion at col. 10, lines 1-3 of Farber suggests that Farber views six days of inhibition as being quite prolonged. Indeed, six days is the longest period of inhibition described in Farber.

Farber is cited in the Office action as teaching that "agents may be added to the substrate by spraying, dipping, soaking or by incorporated [*sic*] directly into the substrate material of the device." However, while it is agreed that Faber states that "[t]he slime inhibitor may be added to the material on which microbial growth is to be inhibited by ... incorporation into the material itself" (see, col. 4, lines 34-37), it is unclear what is being disclosed or suggested by this language, for instance, with respect to the location of slime inhibitor (e.g., whether it is incorporated *throughout* the material as claimed in claims 1 and 72, whether it is incorporated at the surface of the material, etc.).

Darouiche fails to make up for the above noted deficiencies in Terry and Farber. For example, Darouiche is directed to biofilm penetrating agents, in particular, cysteine and derivatives thereof (see, col. 6, lines 18 *et seq.*). Claims 1 and 72, on the other hand, both require the combination of (a) an antimicrobial agent and (b) a microbial attachment/biofilm synthesis inhibitor selected from NSAIDs, chelating agents, and mixtures thereof. Hence, as with Terry and Farber above, the use of these materials, in combination, for purposes of inhibiting microbial growth on medical devices, is neither taught nor suggested by Darouiche.

Furthermore, the devices of claims 1 and 72, contain at least one biocompatible matrix polymer region (which comprises one or more polymers and one or more bioactive agents), which is *not* a medical device coating. However, Darouiche, like Terry and Farber above, provides no motivation to provide such a region. Indeed, Darouiche specifically teaches using the disclosed biofilm penetrating agents within a medical device *coating*. See Darouiche Abstract. Hence, the use of a biocompatible matrix polymer region, which is not a medical device coating, and which contains one or more bioactive agent dispersed throughout, is neither taught nor suggested by Darouiche, Terry and/or Farber.

Finally, like Terry and Farber above, Darouiche neither teaches nor suggests a medical device that is effective to inhibit microbial growth on the device for a period of

at least 30 days after implantation or insertion of the device into a subject, as claimed in claims 1 and 72.

For at least the above reasons, it is respectfully submitted that claims 1 and 72 are neither anticipated by, nor obvious in view of, Terry, Farber and Darouiche. Claims 2-4, 6-8, 13-19 and 73-80 depend either directly or indirectly from claim 1 or claim 72 and are therefore patentable over Terry, Farber and Darouiche for at least the same reasons as are claims 1 and 72.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4, 6-8, 13-19 and 72-80 under 35 U.S.C. 103(a) are respectfully requested.

B. Terry in view of Farber and Darouiche and in view of Helmus or Zaffaroni

Claims 9-12, 26-42, 70 and 71 are presently rejected under 35 U.S.C. 103(a) as being unpatentable over Terry in view of Farber and Darouiche (as above) and further in view of Helmus (U.S. Patent No. 5,569,463) or Zaffaroni (U.S. Patent No. 4,036,227).

Applicants respectfully traverse this rejection and its supporting remarks.

For example, as noted above, each of claims 1 and 72 is patentable over Terry in view of Farber and Darouiche. For example, these references neither teach nor suggest a medical device: (a) that comprises, in combination, for purposes of inhibiting microbial growth on the medical device: (i) an antimicrobial agent and (ii) a microbial attachment/biofilm synthesis inhibitor selected from NSAIDs, chelating agents, and mixtures thereof, (b) that contains bioactive agents in an amount effective to inhibit microbial growth on the device for a period of at least 30 days after implantation or insertion of the device into a subject, (c) that contains at least one biocompatible matrix polymer region, which is not a coating, and which contains one or more bioactive agent dispersed throughout.

Helmus and Zaffaroni, which are argued in the Office Action to contain various teachings vis-à-vis ethylene vinyl acetate copolymers, barrier layers[1] and certain medical devices, do not make up for the above-noted deficiencies in Terry, Farber and Darouiche.

[1] It is noted that Zaffaroni is directed to osmotic devices, including oral devices, which are comprised of a wall surrounding and forming a compartment (as a means for containing a useful agent)and having a passageway for releasing the agent. See Zaffaroni Abstract.

For at least these reasons it is respectfully submitted that independent claims 1 and 72 are patentable over Terry in view of Farber and Darouiche and further in view of Helmus or Zaffaroni. Claims 9-12, 26-42, 70 and 71 depend either directly or indirectly from claim 1 and are therefore patentable over Terry, Farber, Darouiche, Helmus and Zaffaroni for at least the same reasons as claim 1.

Accordingly reconsideration and withdrawal of the rejection of claims 9-12, 26-42, 70 and 71 under 35 U.S.C. 103(a) are respectfully requested.

C. Terry in view of Farber and Darouiche and further in view of Braden

Claims 20-22 are presently rejected under 35 U.S.C. 103(a) as being unpatentable over Terry in view of Farber and Darouiche (as above) and further in view of Braden (U.S. Patent No.5,468,787).

Applicants respectfully traverse this rejection and its supporting remarks.

For example, as noted above each of claims 1 and 72 is patentable over Terry in view of Farber and Darouiche. Braden, which is argued in the Office Action to contain various teachings vis-à-vis a base matrix having a radioopacifying agent incorporated therewith, does not make up for the above deficiencies in Terry, Farber and Darouiche.

For at least these reasons, it is respectfully submitted that independent claims 1 and 72 are patentable over Terry in view of Farber and Darouiche and further in view of Braden. Claims 20-22 depend either directly or indirectly from claim 1 and are therefore patentable over Terry, Farber, Darouiche and Braden for at least the same reasons as claim 1.

Accordingly reconsideration and withdrawal of the rejection of claims 20-22 under 35 U.S.C. 103(a) are respectfully requested.

D. Terry in view of Farber and Darouiche and further in view of Capelli

Claims 23-25 are presently rejected under 35 U.S.C. 103(a) as being unpatentable over Terry in view of Farber and Darouiche (as above) and further in view of Capelli (U.S. Patent No. 5,607,683).

Applicants respectfully traverse this rejection and its supporting remarks.

For example, as noted above each of claims 1 and 72 is patentable over Terry in view of Farber and Darouiche. Capelli, which is cited for is disclosure of various therapeutic agents[2], does not make up for the above deficiencies in Terry, Farber and Darouiche

For at least the above reasons it is respectfully submitted that independent claims 1 and 72 are patentable over Terry in view of Farber and Darouiche and further in view of Capelli. Claims 23-25 depend either directly or indirectly from claim 1 and are therefore patentable over Terry, Farber, Darouiche, and Capelli for at least the same reasons as claim 1.

Accordingly reconsideration and withdrawal of the rejection of claims 23-25 under 35 U.S.C. 103(a) are respectfully requested.

E. Terry in view of Farber and Darouiche and further in view of Redkar

Claims 43-47 are presently rejected under 35 U.S.C. 103(a) as being unpatentable over Terry in view of Farber and Darouiche (as above) and further in view of Redkar (U.S. Patent No.6,482,830).

Applicants respectfully traverse this rejection and its supporting remarks.

For example, as noted above each of claims 1 and 72 is patentable over Terry in view of Farber and Darouiche. Redkar does not make up for the above deficiencies in Terry, Farber and Darouiche.

Moreover, Redkar, which is directed to compositions and formulations containing 9-nitrocamptothecin polymorphs, is cited in the Office Action for its disclosure of "the use of a catheter or a stent for treatment of the pancreas wherein the device comprises a bicarbonate buffering agent." However, it is not seen where such a teaching is found in Redkar. The Office is again requested to point out the specific teachings in Redkar upon

[2] Capelli was apparently cited for its teaching of various therapeutic agents, including cisplatin. It is noted, however, that cisplatin is apparently only mentioned in the background of the invention. Furthermore, it is noted that Capelli is directed to "compositions [that] are useful for topical treatment of infections caused by bacteria, fungus and viruses in humans and animals and for *treating* medical devices, foams and adhesives to impart infection-resistance." See Capelli Abstract (emphasis added). Hence, Capelli is drawn to treating preexisting device structures to impart infection-resistance.

which it is relying for support of this proposition, so that a proper response can be considered.

For at least the above reasons, it is respectfully submitted that independent claims 1 and 72 are patentable over Terry in view of Farber and Darouiche and further in view of Redkar. Claims 43-47 depend either directly or indirectly from claim 1 and are therefore patentable over Terry, Farber, Darouiche and Redkar for at least the same reasons as claim 1.

Accordingly reconsideration and withdrawal of the rejection of claims 43-47 under 35 U.S.C. 103(a) are respectfully requested.

F. Terry in view of Farber and Darouiche and further in view of Capelli

Claims 72-76 are presently rejected under 35 U.S.C. 103(a) as being unpatentable over Terry in view of Farber and Darouiche (as above) and further in view of Helmus, Zaffaroni and Braden.

Applicants respectfully traverse this rejection and its supporting remarks.

For example, as noted above each of claims 1 and 72 is patentable over Terry in view of Farber and Darouiche and further in view of Helmus, Zaffaroni and/or Braden.

Claims 73-76 depend either directly or indirectly from claim 72 and are therefore patentable over Terry, Farber, Darouiche, Helmus, Zaffaroni and Braden for at least the same reasons as claim 72.

Accordingly reconsideration and withdrawal of the rejection of claims 72-76 under 35 U.S.C. 103(a) are respectfully requested.

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited.

FEES

The Office is authorized to charge any fees required, to deposit account number 50-1047.

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